those cases it was very conveniently purified by passing its solution in benzene over a column of alumina.[17] The same weight of alumina as of compound was sufficient to remove any color from the ketone. Elution with benzene and benzene–ether gave the perfectly white ketone (V) m. p. 99–100°,[4,6] which was thus obtained in 85% yield.

γ-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-butyric Acid (VIII).—Attempts to add only one mole of hydrogen to IV were unsuccessful with Adams platinum oxide catalyst as well as with a 5% palladium–barium sulfate catalyst. Raney nickel proved satisfactory for our purpose: To a solution of 0.23 g. of ester (IV) in 10 ml. of absolute alcohol was added 0.21 g. of Raney nickel catalyst[18] (wet with alcohol) and the mixture was reduced with hydrogen in a low pressure apparatus. After half an hour, the theoretical quantity of hydrogen for reduction of one double bond had been absorbed and the rate of hydrogenation had slowed down considerably.

After removal of the catalyst, the ester was hydrolyzed and worked up exactly as described above for the ester of VI, giving 0.16 g. of the acid (VIII), m. p. 73–74°. The absorption spectrum of this compound is shown on Fig. 1, curve 2.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.22; H, 7.65.

1-Keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VII).—A solution of 50 mg. of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-butyric acid (VIII) in 0.5 ml. of glacial acetic acid and 1 ml. of acetic anhydride was treated with 0.5 ml. of an acetic acid solution containing 20 mg./ml. of zinc chloride (fused)[14] and heated under nitrogen for four hours. The mixture was evaporated on the steam-bath after addition of methanol, and the residue was heated on the steam-bath under nitrogen for thirty minutes with 8 ml. of 5% potassium hydroxide solution. The non-acidic, insoluble material was taken up in ether, and the oil remaining after evaporation of the solvent was heated for thirty minutes with an excess of semicarbazide hydrochloride in methanol in the presence of a little pyridine. In this manner, 35 mg. of semicarbazone was obtained, m. p. 248–249°, dec. (when introduced in the heating-bath at 210°). This is higher than the m. p. previously reported for this compound (238–240°, dec.)[19] so that it was considered necessary to prepare the 2,4-dinitrophenylhydrazone of the ketone: The semicarbazone obtained above was heated for a few minutes with 12% hydrochloric acid on the steam-bath, and the yellow, fluorescent solution was extracted with ether. The oil remaining after removal of the ether was evaporatively distilled under a high vacuum, but the ketone (VII) obtained in this way was still an oil (the difficulty of crystallizing the ketone has been noted previously[15,19]). Treatment with 2,4-dinitrophenylhydrazine in alcohol, in the presence of a trace of sulfuric acid, gave after short heating on the water-bath the iodine colored, characteristic dinitrophenylhydrazone, m. p. 245–247°. On recrystallization from toluene this gave small needles, m. p. 250–252° (reported m. p. 256°,[15] 253–255°[20]). To remove any doubts about the identity of the substance, it was analyzed with the following results: Calcd. for $C_{21}H_{20}N_4O_5$: C, 61.75; H, 4.93. Found: C, 61.49; H, 5.17.

Acknowledgment.—The author wishes to thank Dr. Elkan R. Blout of Polaroid Corporation for arranging for the determination of the absorption spectra reported in this paper.

Summary

Methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-crotonate has been prepared by the reaction of 6-methoxy-α-tetralone and methyl γ-bromocrotonate in the presence of zinc. This compound was isomerized to methyl γ-(6-methoxy-1-naphthyl)-butyrate by heating with palladium–charcoal. The acid obtained from that compound on hydrolysis was cyclized with hydrogen fluoride to the equilenin intermediate 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene.

Partial reduction of methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-crotonate was successfully accomplished with Raney nickel at atmospheric pressure and room temperature, and the resulting ester was hydrolyzed and cyclized to 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.

(17) Aluminum Co. of America, grade F-20, minus 80 mesh.

(18) "Organic Syntheses," Vol. 21, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

(19) Robinson and Walker, *J. Chem. Soc.*, 60 (1937).

(20) Hewett, *J. Chem. Soc.*, 50 (1936).

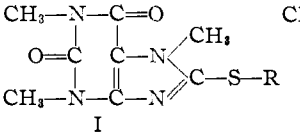
CAMBRIDGE, MASS. RECEIVED MARCH 31, 1947

[CONTRIBUTION FROM THE RESARCH LABORATORIES OF PARKE, DAVIS AND CO.]

8-R-Thio- and 8-R-Sulfonylcaffeine Derivatives

BY LOREN M. LONG

During the course of our search for compounds possessing anticonvulsant activity, it became desirable to synthesize a number of 8-substituted caffeine derivatives of the type represented by (I) and (II) where R may be a simple alkyl, substituted alkyl or an aryl group.



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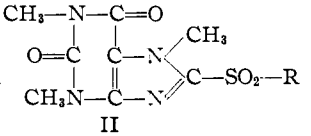


II

Numerous cyclic ureides such as barbituric acids and hydantoins exhibit the property of raising the convulsive threshold in animals in which convulsive seizures are electrically induced.[1] Although most of these compounds contain at least one phenyl radical, there are several which contain only simple alkyls as substituents. Moreover, the substitution of a methyl radical on the urea portion of the molecule has at times proved to be advantageous.[2] That substitution in the 8-position of caffeine does not necessarily yield physiologically inert compounds is evidenced by the

(1) Merritt and Putnam, *Epilepsia*, **3**, 51 (1945).

(2) Lascalzo, *J. Nervous Mental Disease*, **101**, 537 (1945); Goodman and Manuel, *Fed. Proc.*, IV No. 1, 119 (1945); Everett and Richards, *ibid.*, IV No. 1 20 (1945).

TABLE I

8-R-THIO- AND 8-R-SULFONYLCAFFEINE DERIVATIVES

	8-R-Thiocaffeine						8-R-Sulfonylcaffeine				
R[a]	Yield, %	M. p., °C.	Formula	Nitrogen, %[b] Calcd.	Found	R[a]	Yield, %	M. p., °C.	Formula	Nitrogen, %[b] Calcd.	Found
Methyl[c]	65	185	$C_9H_{12}N_4O_2S$	23.32	23.36	Methyl	60	219	$C_9H_{12}N_4O_4S$	20.58	20.53
Ethyl[c]	70	138–139.5	$C_{10}H_{14}N_4O_2S$	22.03	22.11	Ethyl	68	157.5	$C_{10}H_{14}N_4O_4S$	19.57	19.55
n-Propyl	74.5	131	$C_{11}H_{16}N_4O_2S$	20.88	20.60	*n*-Propyl	75	133	$C_{11}H_{16}N_4O_4S$	18.66	18.64
Isopropyl	73	126–128	$C_{11}H_{16}N_4O_2S$	20.88	20.92	Isopropyl	73	153	$C_{11}H_{16}N_4O_4S$	18.66	18.48
n-Butyl	80	70–73	$C_{12}H_{18}N_4O_2S$	19.84	19.94	*n*-Butyl	80	127.5	$C_{12}H_{18}N_4O_4S$	17.82	17.85
Benzyl	89	149.5	$C_{15}H_{16}N_4O_2S$	17.71	17.75	Benzyl	92	209	$C_{15}H_{16}N_4O_4S$	16.08	15.93
Phenyl	90	147	$C_{14}H_{14}N_4O_2S$	18.55	18.39	Phenyl	87	230	$C_{14}H_{14}N_4O_4S$	16.76	16.91
β-Amino-β-carboxyethyl	57	297 (dec.)	$C_{11}H_{15}N_5O_4S$	22.35	22.20						

[a] See formulas I and II. [b] The analytical data reported in this paper were determined by Miss Constance Turner. [c] See ref. 6.

activity of 8-ethoxycaffeine,[3] a compound possessing analgetic and local anesthetic properties.

An appreciable number of caffeine derivatives of the type represented by (I) in which sulfur is replaced by oxygen has been prepared. Fischer[4] and especially Huston[5] have investigated the preparation and properties of these compounds rather thoroughly. However, very few of the 8-R-thiocaffeines and none of the 8-R-sulfonylcaffeines have been prepared. Biltz and co-workers[6] have prepared 8-methyl, 8-ethyl, 8-allyl and 8-carboxymethylthiocaffeine as well as the corresponding 2-thio derivatives of the first three.

Although Biltz prepared the 8-R-thiocaffeine derivatives from 8-caffeinethiol and alkyl halides, it was thought that a modification of the method used by Fischer[4] for the preparation of 8-alkoxycaffeine would be more suitable. Accordingly, 8-chlorocaffeine was treated with the sodium salts of mercaptans using 50% aqueous ethanol as the solvent. The yields obtained were good, indicating again that, unlike the preparation of alkoxy compounds which often requires anhydrous media[5] synthesis of alkylthio derivatives proceeds without difficulty in aqueous solvents.[7] A summary of the compounds thus prepared is given in Table I.

Oxidation of the 8-R-thiocaffeine derivatives to the corresponding sulfones was accomplished by the use of hydrogen peroxide in glacial acetic acid and acetic anhydride. Oxidation of the cysteine derivative was not attempted because of the presence of a free amino group, though such a reaction is sometimes successful since acetylation of the amino group occurs during the oxidation.

Pharmacology.—Preliminary investigation indicates that both the 8-R-thio- and the 8-R-sulfonylcaffeine derivatives are inactive in giving protection against electrically induced convulsions.

(3) Filehne, *Arch. Anat. Physiol.*, **133**, 84 (1886).

(4) Fischer, *Ann.*, **215**, 267 (1882).

(5) Huston and Allen, THIS JOURNAL, **56**, 1356 (1934).

(6) Biltz and Beck, *J. Prakt. Chem.*, **118**, 198 (1928); Biltz and Sauer, *Ber.*, **64**, 752 (1931); Biltz and Rakett, *ibid.*, **61**, 1409 (1928).

(7) Long, THIS JOURNAL, **68**, 2159 (1946).

Experimental

8-Chlorocaffeine.—The method employed is essentially that of Fischer and Reese.[8] A mixture of 194 g. (1.0 mole) of dry caffeine and 1200 ml. of chloroform was prepared in a flask fitted with an inlet tube and a reflux condenser and heated to reflux. A fairly rapid stream of dry chlorine was passed into the hot solution until the solid which first precipitated had dissolved (one and one-half hours). Most of the solvent was distilled off on the steam-bath and the remainder was removed *in vacuo*. The residue represents an almost quantitative yield of 8-chlorocaffeine and is suitable for use as an intermediate without further purification.

8-*n*-Propylthiocaffeine.—To a cold solution of 8 g. (0.2 mole) of sodium hydroxide in 350 ml. of 50% aqueous ethanol was added 15.2 g. (0.2 mole) of 1-propanethiol. The solution was stirred and 46.7 g. (0.2 mole) of 8-chlorocaffeine was added rapidly. On heating to reflux a clear solution was obtained which was refluxed for an hour. When the solution was cooled in an ice-bath, the product precipitated as a crystalline solid. It was filtered off, dried *in vacuo* at 60°, then recrystallized with small loss of material from aqueous ethanol.

8-(β-Amino-β-carboxyethyl)-thiocaffeine.—Eleven and four-tenths grams (0.05 mole) of 8-chlorocaffeine was added to a solution of 7.9 g. (0.05 mole) of cysteine hydrochloride in 100 ml. of 50% aqueous ethanol. Six grams (0.15 mole) of sodium hydroxide was quickly added and the mixture was refluxed for an hour. The hot mixture was filtered and 0.05 mole of dilute hydrochloric acid was added to the filtrate. There was no precipitation. The filtrate was diluted with 500 ml. of ethanol and left in the icebox for several days. A solid precipitated which was filtered off and dried. It weighed 10 g. and decomposed at 290°. Recrystallization was carried out by solution in 200 ml. of boiling water, charcoaling and filtering. On cooling, the product crystallized in needle form.

8-*n*-Propylsulfonylcaffeine.—Thirteen and four-tenths grams (0.05 mole) of 8-*n*-propylthiocaffeine was mixed with 100 ml. of glacial acetic acid and 25 ml. of acetic anhydride in an Erlenmeyer flask. To the mixture was added 25 ml. of 30% hydrogen peroxide. The temperature slowly increased to 60° at which point the flask was cooled in an ice-bath enough to keep the temperature below 80°. After two hours the clear solution was diluted with two volumes of cold water. Since precipitation of product did not occur after extensive cooling, the solution was evaporated to dryness on a water-bath at reduced pressure. Care must be taken not to apply excessive heat as the residue may contain acetyl peroxide. The solid residue was recrystallized from 95% ethanol.

Summary

A series of eight 8-R-thiocaffeine derivatives has been prepared and, with the exception of one

(8) Fischer and Reese, *Ann.*, **221**, 336 (1883).

member, oxidized to the corresponding sulfone series.

Preliminary testing indicates that the compounds are inactive against electrically induced convulsions.

DETROIT, MICHIGAN RECEIVED MAY 14, 1947

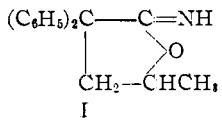
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

A New Synthesis and Confirmation of the Structure of Amidone[1]

BY NELSON R. EASTON, JOHN H. GARDNER AND JOSEPH R. STEVENS

The original procedure for the synthesis of the new German analgesic, Amidone or 10820,[2] involves some technical difficulties due to the formation of isomeric aminonitriles in approximately equal amounts.[3] A new synthesis which avoids this difficulty has been developed.

Diphenylacetonitrile was condensed with propylene oxide in the presence of sodium amide to yield 3,3-diphenyl-5-methyltetrahydro-2-furanoneimine (I), which was isolated as the hydrochloride. On treating this compound with phosphorus tribromide, 4-bromo-2,2-diphenylpentanenitrile (II) was formed. The analogous chlorine compound (III) was prepared in a similar manner. Either of these halonitriles, condensed with dimethylamine, gave 4-dimethylamino-2,2-diphenylpentanenitrile (IV), from which Amidone was prepared by the action of ethylmagnesium bromide, as in the original synthesis.[2]



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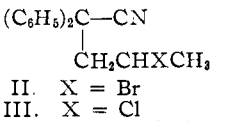
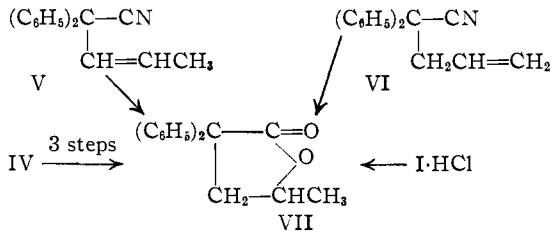


II. X = Br
III. X = Cl
IV. X = $N(CH_3)_2$

The yields in the formation of the aminonitrile from either of the halonitriles under the conditions tried so far have been below 10%. This reaction is being studied further. There was always formed as a major product an unsaturated nitrile, presumably 2,2-diphenyl-3-pentenenitrile (V) or a mixture of that with 2,2-diphenyl-4-pentenenitrile (VI). The product agreed with the latter in all properties except refractive dispersion.

As an incidental part of this work, the structure established for Amidone by Schultz, Robb and Sprague was confirmed by a new series of reactions. 4-Dimethylamino-2,2-diphenylpentane-nitrile (IV) was degraded by exhaustive methylation to an unsaturated nitrile[3] (V, VI or a mixture) which was hydrolyzed without purification to the lactone of 2,2-diphenyl-4-hydroxypentanoic acid (VII). The same lactone was also formed by the hydrolysis both of 2,2-diphenyl-4-pentenenitrile (VI) and of the unsaturated nitrile obtained as a by-product in the new synthesis of the aminonitrile (IV). The hydrochloride of 3,3-diphenyl-5-methyltetrahydro-2-furanoneimine (I) gave the same lactone on long standing in aqueous solution. These facts can only be accounted for by a straight chain structure for the aminonitrile (IV).



Experimental

3,3-Diphenyl-5-methyltetrahydro-2-furanoneimine Hydrochloride (I).—To a well-stirred suspension of 20 g. of sodium amide in 100 ml. of benzene there was added 96 g. of diphenylacetonitrile. The mixture was heated to 40–45° for one and a half hours and then cooled to 20°, 29 g. of propylene oxide then was added, with the temperature kept at 20–25°. The mixture was then boiled for fifteen minutes and poured into a large excess of water. The benzene layer was separated and dried over magnesium sulfate. The mixture was filtered and 75 g. of a 38% solution of anhydrous hydrogen chloride in absolute alcohol and 500 ml. of anhydrous ether were added to the filtrate. The mixture was placed in a refrigerator for sixteen hours and then filtered. The yield of material melting at 220–222° with decomposition was 114 g. (80%).

Anal. Calcd. for $C_{17}H_{18}NOCl$: N, 4.87; Cl, 12.32. Found: N, 4.87; Cl, 12.20.

A portion of the hydrochloride was suspended in water and an excess of sodium hydroxide was added. A solid separated which melted at 115–116° after crystallization from methylcyclohexane.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.45; H, 6.81; N, 5.55.

4-Bromo-2,2-diphenylpentanenitrile (II).—A mixture of 112 g. of the hydrochloride (I) and 224 g. of phosphorus tribromide was refluxed for thirty minutes. After cooling, 200 cc. of benzene was added and the mixture was filtered. The filtrate was poured into an excess of water, the benzene layer separated, washed with water and dried over magnesium sulfate. The benzene solution was then evaporated to dryness under reduced pressure, leaving 107.6 g. of material melting at 41–42°. Analysis showed that this material was quite pure.

Anal. Calcd. for $C_{17}H_{16}NBr$: C, 64.98; H, 5.13; N, 4.46. Found: C, 65.05; H, 5.05; N, 4.52.

4-Chloro-2,2-diphenylpentanenitrile (III).—A mixture of 24 g. of the hydrochloride (I), 40 ml. of phosphorus trichloride and 40 ml. of phosphorus oxychloride was heated in sealed tubes at 175° for three hours. The tubes were opened and their contents poured into water. The resulting mixture was extracted with benzene. The benzene layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The yield

(1) Presented before the Division of Medicinal Chemistry, American Chemical Society, Atlantic City, N. J., April 16, 1947.

(2) Office of the Publication Board, Department of Commerce, Report PB 981, p. 96.

(3) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188 (1947); W. R. Brode and M. W. Hill, *ibid.*, **69**, 724 (1947).